PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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19. Aug. 2004

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/003164	25.03.2004	26.03.2003

International Patent Classification (IPC) or both national classification and IPC
C12N7/04, A61K39/00, A61K39/39, C12N15/11

B1	HJW
B2	
B3	
Sekr.	SA
EDV	
Ablg.	

Applicant
CYTOS BIOTECHNOLOGY AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

20.1.2005

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/003164

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2, 11-16, 19-43, 45, 47, 54-61, 63-87, 96
	No:	Claims	1, 3-10, 17-18, 44, 46, 48-53, 62, 88-95, 97-98
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-98
Industrial applicability (IA)	Yes:	Claims	1-98
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/003164

Re Item II
Priority

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The present application discloses a composition comprising a virus-like particle, at least one immunostimulatory substance and at least one antigen or antigenic determinant which comprises a human melanoma MelanA peptide analogue and methods for enhancing an immune response in an animal using said composition.

2. Reference is made to the following documents :

D1: WO 01/16320 A (LUDWIG INST CANCER RES) 8 March 2001 (2001-03-08)
D2: US-B-6 326 2001 (ROMERO PEDRO ET AL) 4 December 2001 (2001-12-04)
D3: LECHNER F ET AL: "VIRUS-LIKE PARTICLES AS A MODULAR SYSTEM FOR NOVEL VACCINES" INTERVIROLOGY, XX, XX, vol. 45, no. 4-6, July 2002 (2002-07), pages 212-217.
D4: BROWN W L ET AL: "RNA BACTERIOPHAGE CAPSID-MEDIATED DRUG DELIVERY AND EPITOPE PRESENTATION" INTERVIROLOGY, XX, XX, vol. 45, no. 4 - 6, July 2002 (2002-07), pages 371-380.
D5: GILBERT ET AL: "A protein particle vaccine containing multiple malaria epitopes" NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 15, 1 November 1997 (1997-11-01), pages 1280-1284.
D6: FEHR T ET AL: "T cell-independent type I antibody response against B cell epitopes expressed repetitively on recombinant virus particles" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 95, no. 16, 4 August 1998 (1998-08-04), pages 9477-9481.
D7: OXENIUS A ET AL: "CpG-containing oligonucleotides are efficient adjuvants for induction of protective antiviral immune responses with T-cell peptide vaccines" JOURNAL OF VIROLOGY, THE AMERICAN SOCIETY FOR MICROBIOLOGY, US, vol. 73, no. 5, May 1999 (1999-05), pages 4120-

4126.

D8: US 2003/050268 A1 (BERG DANIEL J ET AL) 13 March 2003 (2003-03-13)

3. Lack of novelty; article 33(2) PCT.

3.1 The document D1 discloses Melan A nona- and decapeptides which bind to HLA molecules and the use of these antigens. Some of the peptides disclosed in D1 are the same as the peptides disclosed in the present application. The correspondence is given below :

D1 (WO 01/16320)	Present application :
SEQ ID NO: 6 (Example 3)	SEQ ID NO: 88
SEQ ID NO: 7 (Example 3)	SEQ ID NO: 89
SEQ ID NO: 11 (Example 6)	SEQ ID NO: 84
SEQ ID NO: 13 (Example 6)	SEQ ID NO: 50
SEQ ID NO: 14 (Example 6)	SEQ ID NO: 87
SEQ ID NO: 16 (Example 6)	SEQ ID NO: 86

D1 also discloses the possibility to introduce of DNA encoding said epitopes in Ty virus-like particles (p. 38, lines 18-21 and reference Gilbert et al.).

The ISA is the opinion that the molecules building the VLPs can be considered as immunostimulatory substance. Therefore, the ISA is the opinion that the subject-matter of claims 1, 3-10, 17-18, 44, 46, 48-53, 62, 88-95 and 97-98 cannot be considered as novel in the sense of article 33(2) PCT.

3.2 The teaching of D2 is almost the same as the teaching of D1 with the following peptides disclosed.

D2 (US-B-6 326 2001)	Present application.
SEQ ID NO:1 (Table 1)	SEQ ID NO: 84
SEQ ID NO: 8 (Table 1)	SEQ ID NO: 85
SEQ ID NO: 9 (Table 1)	SEQ ID NO: 50
SEQ ID NO: 10 (Table 1)	SEQ ID NO: 87

SEQ ID NO: 12 (Table 1)	SEQ ID NO: 86
SEQ ID NO: 13 (Table 1)	SEQ ID NO: 88
SEQ ID NO: 14 (Table 1)	SEQ ID NO: 89.

For the reasons already mentioned in point 3.1 above, the ISA is the opinion that the subject-matter of claims 1, 3-10, 17-18, 44, 46, 48-53, 62, 88-95 and 97-98 cannot be considered as novel over the teaching of D2 in the sense of article 33(2) PCT.

4. Lack of inventive step; article 33(3) PCT.

The documents D1 and D2 disclose Melan A peptide analogues according to the present application and their use for generating in immune response against cancerous cells.

In the light of those documents, the problem to be solved by the present application can be seen as the provision of an improved composition for generating an immune response against cancerous cells.

The application solves this problem by the provision of a composition comprising a virus-like particle (VLP), at least one immunostimulatory substance and at least one MelanA peptide analogue, preferably bound to the VLP through a non-peptide bound between an amino group or a lysine residue and a sulfhydril group or a cysteine residue.

The documents D1 and D2 disclose the possibility to use Ty-VLPs to present the epitopes. Moreover the documents D3-D6 disclose the use of VLPs for presenting B and T-cells epitopes and the enhanced immunity achieved by presenting the epitopes in ordered and repetitive manner.
More precisely : D3 discloses non infectious VLPs and the antigen binding system proposed in the present application. D3 mentions that the antigens coupled to VLP induce strong and long lasting B as well as T cell responses (p. 214, right-hand column, VLP-based vaccines are safe and effective in low amounts, lines 1-4). The use of VLPs in cancer therapy is suggested (p. 216, left-hand column, VLP-based vaccines in immunotherapy, lines 6-9).
D4 discloses RNA bacteriophage capsid VLP which ca be used to present foreign B or T cells epitopes. Moreover D4 discloses that the VLPs can also be used to

protect nucleic acid-based drugs (Abstract). A binding system for the antigens is also disclosed (p. 376-377, Formation of Immuno-Conjugate SVs).
D5 discloses the use of Ty-VLPs as disclosed in D1 and D2.
D6 discloses VLPs based on hepatitis B core antigen (HBcAg) capsids and RNA phage Qβ coats as carriers of foreign epitopes.

The documents D7 and D8 disclose unmethylated CpG oligonucleotides, some of which are claimed in the present application and their use as potent adjuvants for peptide mediated T-cell vaccination.

The ISA is the opinion that the use of VLPs for presenting the antigen cannot be considered as inventive in the light of the teaching of D1 or D2 taken in combination with D3, D4, D5 or D6.

Moreover, the additional use of unmethylated CpG as immunostimulatory adjuvants can also not be considered as inventive.

Therefore, the ISA is the opinion that claims 1-98 of the present application lack inventive step in the sense of article 33(3) PCT.